

FIG.1

Met Gly Val His Glu Cys Pro Ala Trp Leu Trp Leu Leu Ser Leu  
-25 -20 -15

Leu Ser Leu Pro Leu Gly Leu Pro Val Leu Gly Ala Pro Pro Arg Leu  
-10 -5 1 5

Ile Cys Asp Ser Arg Val Leu Glu Arg Tyr Leu Leu Glu Ala Lys Glu  
10 15 20

Ala Glu Asn Ile Thr Thr Gly Cys Ala Glu His Cys Ser Leu Asn Glu  
25 30 35

Asn Ile Thr Val Pro Asp Thr Lys Val Asn Phe Tyr Ala Trp Lys Arg  
40 45 50

Met Glu Val Gly Gln Gln Ala Val Glu Val Trp Gln Gly Leu Ala Leu  
55 60 65

Leu Ser Glu Ala Val Leu Arg Gly Gln Ala Leu Leu Val Asn Ser Ser  
70 75 80 85

Gln Pro Trp Glu Pro Leu Gln Leu His Val Asp Lys Ala Val Ser Gly  
90 95 100

Leu Arg Ser Leu Thr Thr Leu Leu Arg Ala Leu Gly Ala Gln Lys Glu  
105 110 115

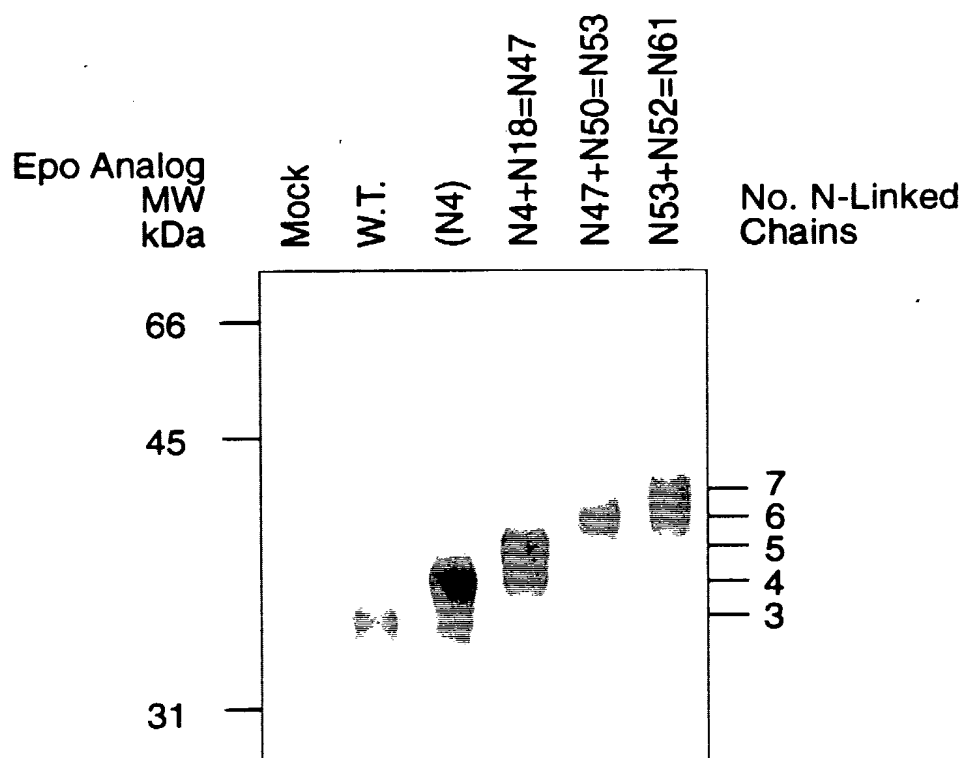
Ala Ile Ser Pro Pro Asp Ala Ala Ser Ala Ala Pro Leu Arg Thr Ile  
120 125 130

Thr Ala Asp Thr Phe Arg Lys Leu Phe Arg Val Tyr Ser Asn Phe Leu  
135 140 145

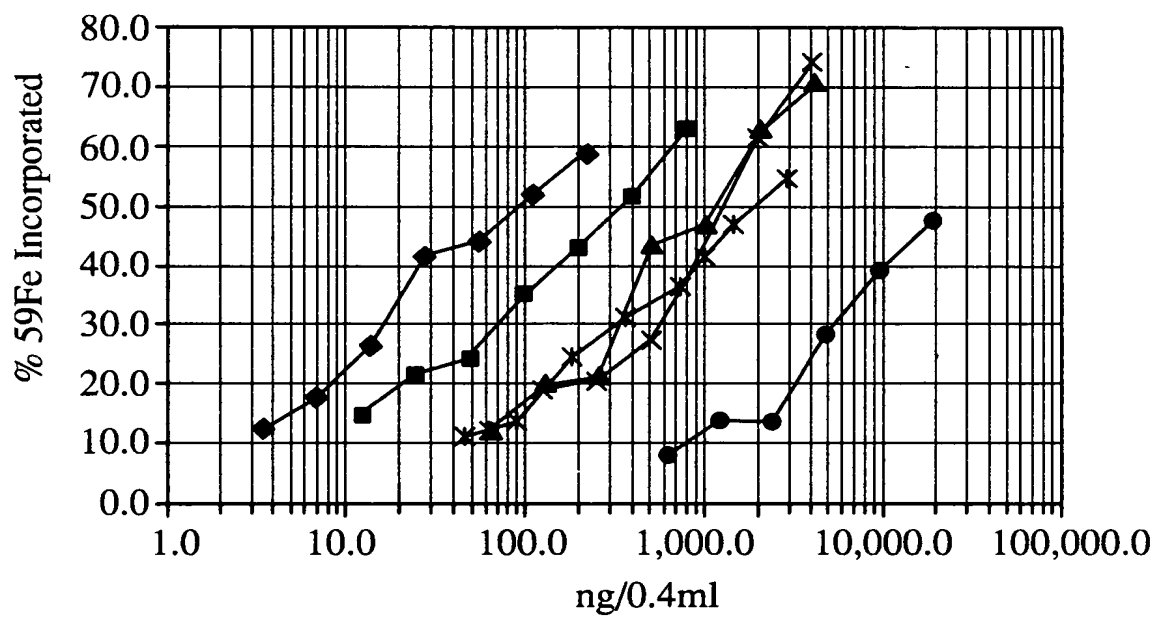
Arg Gly Lys Leu Lys Leu Tyr Thr Gly Glu Ala Cys Arg Thr Gly Asp  
150 155 160 165

Arg

FIG. 2



# FIG. 3



◆ N53      ▲ N4  
 × N18      ● rHuEPO  
 ■ N47  
 \* N50

FIG.4

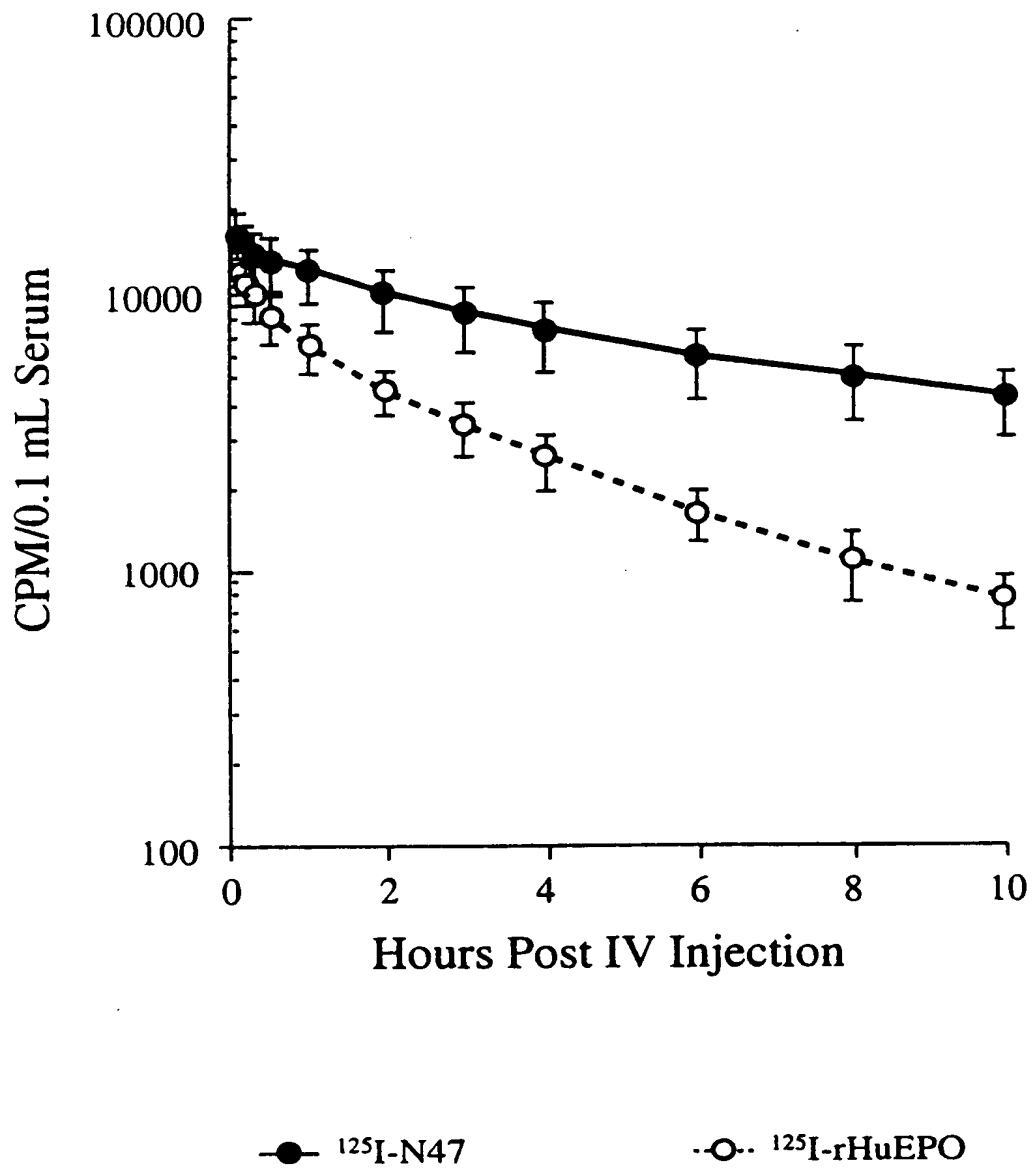


FIG.5

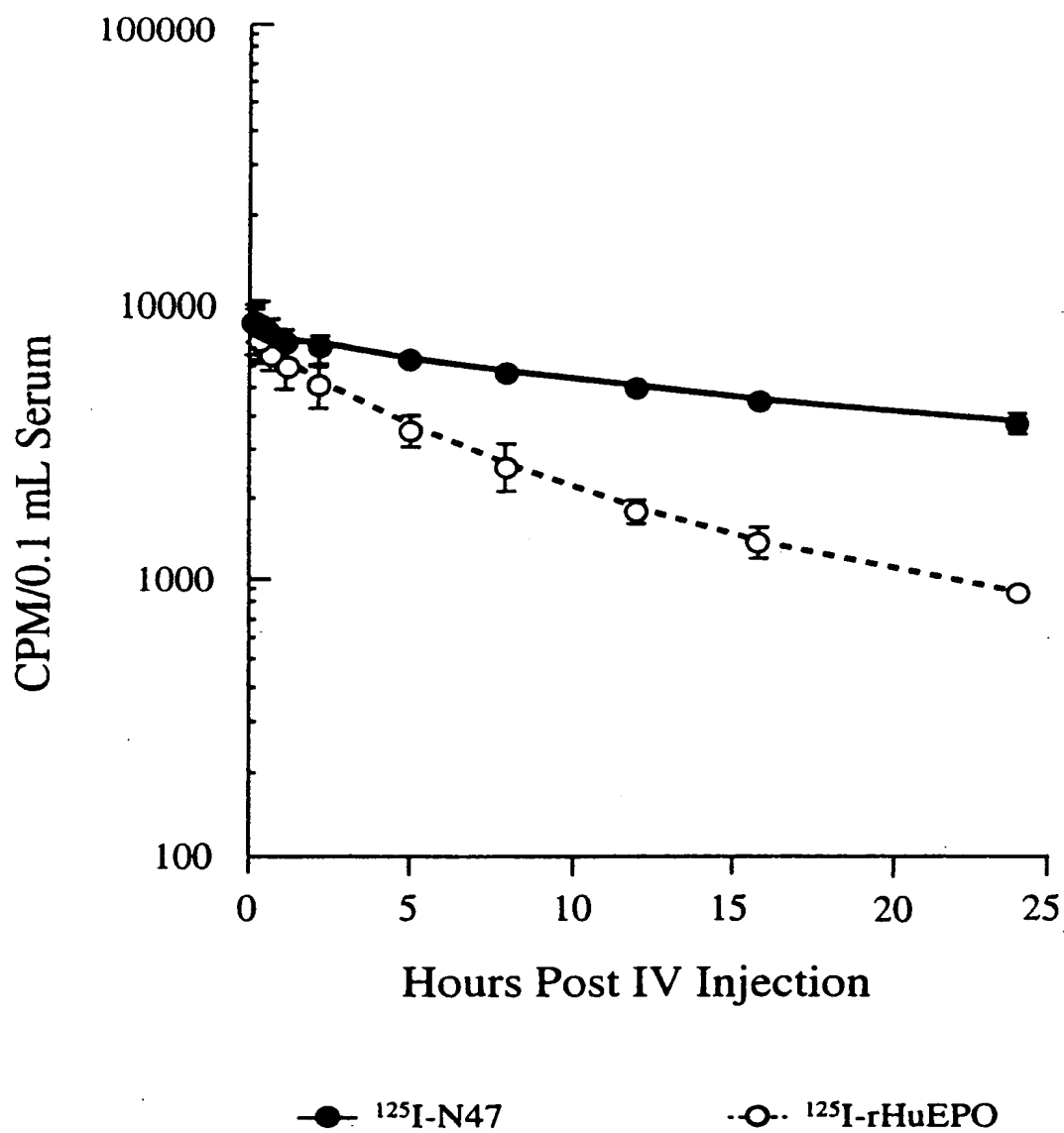
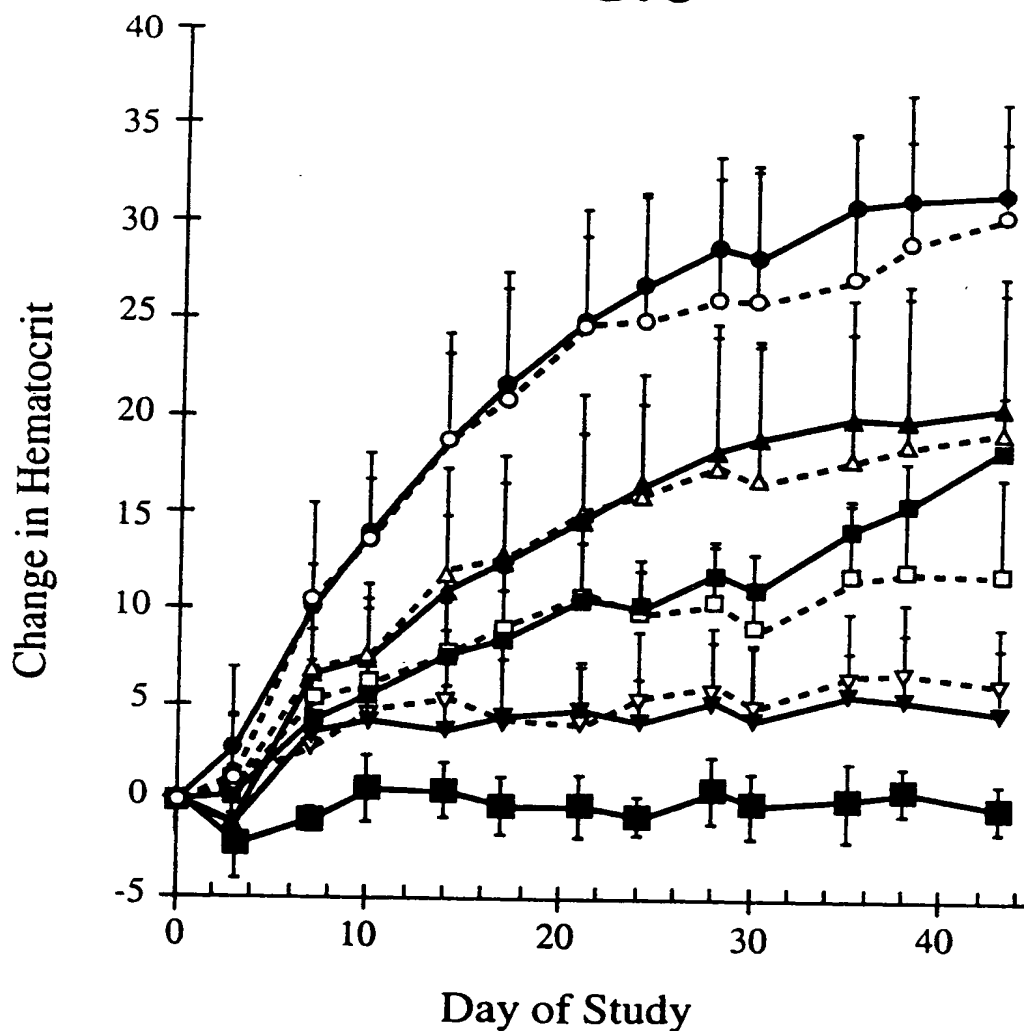


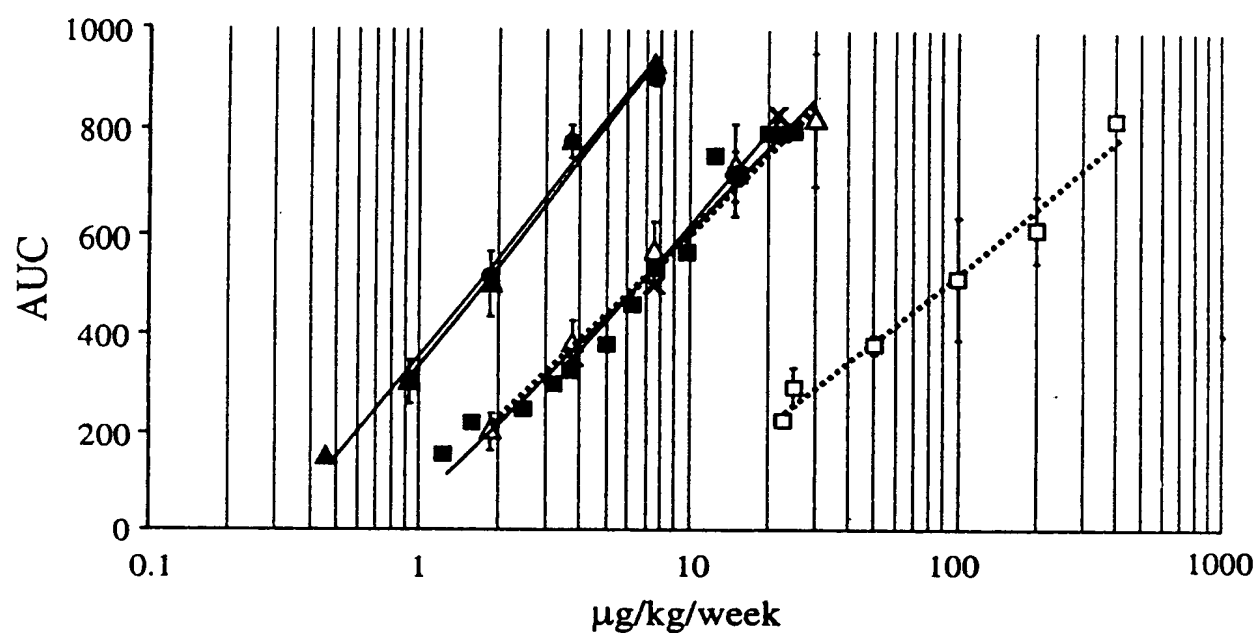
FIG.6



- N47 1.25  $\mu\text{g/kg/dose}$  (IP-TIW)
- ▲ N47 0.625  $\mu\text{g/kg/dose}$  (IP-TIW)
- N47 0.313  $\mu\text{g/kg/dose}$  (IP-TIW)
- ▼ N47 0.156  $\mu\text{g/kg/dose}$  (IP-TIW)
- vehicle (IV-TIW)

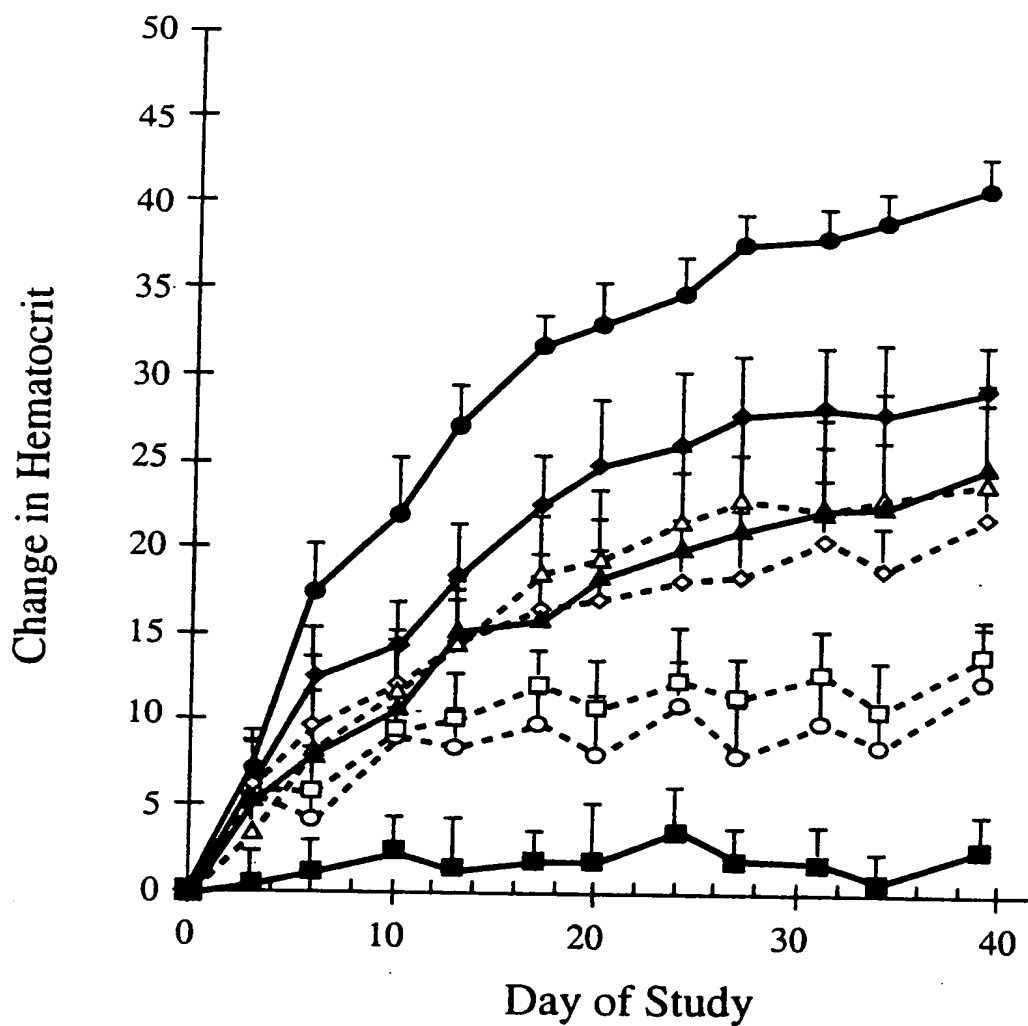
- rHuEPO 10  $\mu\text{g/kg/dose}$  (IP-TIW)
- △ rHuEPO 2.5  $\mu\text{g/kg/dose}$  (IP-TIW)
- rHuEPO 1.25  $\mu\text{g/kg/dose}$  (IP-TIW)
- ▽ rHuEPO 0.625  $\mu\text{g/kg/dose}$  (IP-TIW)

# FIG.7



- N47 (IV TIW)
- ▲ N47 (IP TIW)
- N47 (IV QW)
- × N47 (IP QW)
- △ rHuEPO (IP TIW)
- rHuEPO (IV QW)

FIG.8

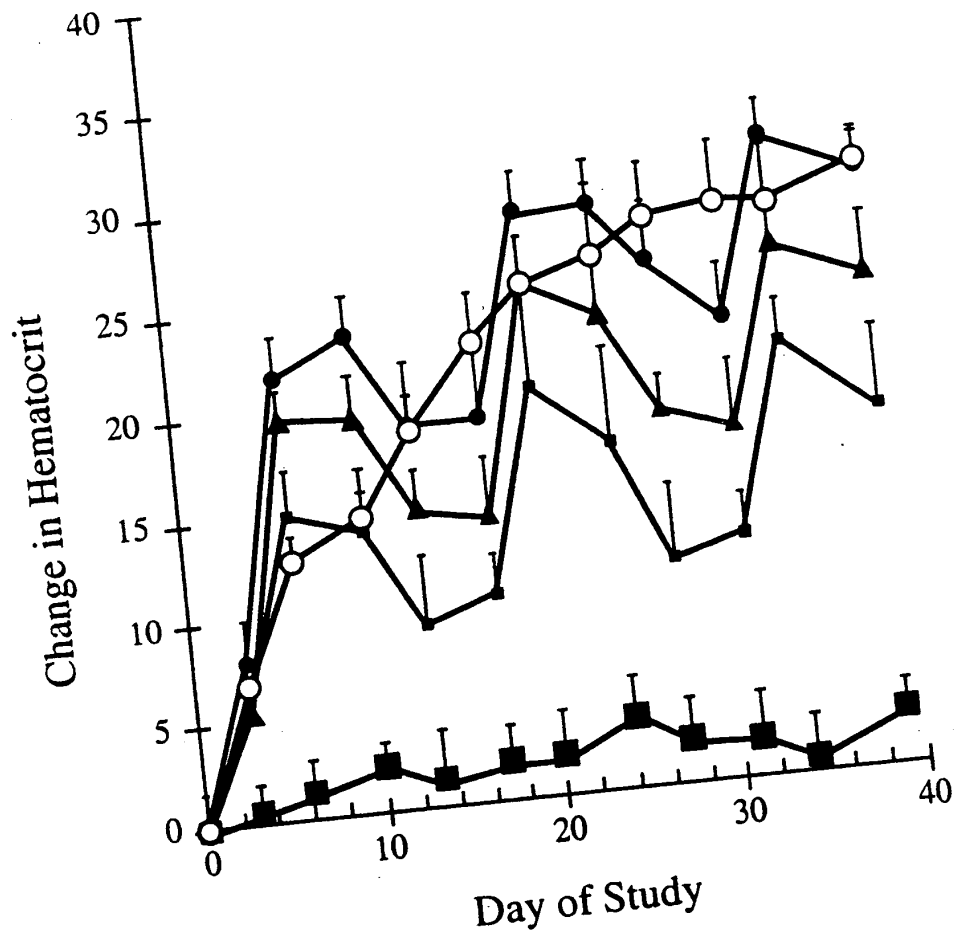


● N47 25 µg/kg/dose (IV-QW)  
 ◆ N47 12.5 µg/kg/dose (IV-QW)  
 ▲ N47 6.25 µg/kg/dose (IV-QW)  
 ■ vehicle (IV-QW)

△ rHuEPO 200 µg/kg/dose (IV-QW)  
 ◇ rHuEPO 100 µg/kg/dose (IV-QW)  
 □ rHuEPO 50 µg/kg/dose (IV-QW)  
 ○ rHuEPO 25 µg/kg/dose (IV-QW)



FIG.9



- N47 200 µg/kg/dose (IV-EOW)
- ▲ N47 100 µg/kg/dose (IV-EOW)
- N47 25 µg/kg/dose (IV-EOW)
- N47 12.5 µg/kg/dose (IV-QW)
- vehicle

**FIG. 10**

**Amino acid sequence of hinge, CH2 and  
CH3 regions human IgGγ1**

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Glu | Pro | Lys | Ser | Cys | Asp | Lys | Thr | His | Thr | Cys | Pro | Pro | Cys | Pro | Ala |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |
| Pro | Glu | Leu | Leu | Gly | Gly | Pro | Ser | Val | Phe | Leu | Phe | Pro | Pro | Lys | Pro |
|     |     |     | 20  |     |     |     |     | 25  |     |     |     |     | 30  |     |     |
| Lys | Asp | Thr | Leu | Met | Ile | Ser | Arg | Thr | Pro | Glu | Val | Thr | Cys | Val | Val |
|     |     | 35  |     |     |     |     | 40  |     |     |     |     | 45  |     |     |     |
| Val | Asp | Val | Ser | His | Glu | Asp | Pro | Glu | Val | Lys | Phe | Asn | Trp | Tyr | Val |
|     | 50  |     |     |     |     | 55  |     |     |     |     | 60  |     |     |     |     |
| Asp | Gly | Val | Glu | Val | His | Asn | Ala | Lys | Thr | Lys | Pro | Arg | Glu | Glu | Gln |
| 65  |     |     |     |     | 70  |     |     |     |     | 75  |     |     |     |     | 80  |
| Tyr | Asn | Ser | Thr | Tyr | Arg | Val | Val | Ser | Val | Leu | Thr | Val | Leu | His | Gln |
|     |     |     |     | 85  |     |     |     |     | 90  |     |     |     |     | 95  |     |
| Asp | Trp | Leu | Asn | Gly | Lys | Glu | Tyr | Lys | Cys | Lys | Val | Ser | Asn | Lys | Ala |
|     |     |     | 100 |     |     |     |     | 105 |     |     |     |     | 110 |     |     |
| Leu | Pro | Ala | Pro | Ile | Glu | Lys | Thr | Ile | Ser | Lys | Ala | Lys | Gly | Gln | Pro |
|     |     | 115 |     |     |     |     | 120 |     |     |     |     | 125 |     |     |     |
| Arg | Glu | Pro | Gln | Val | Tyr | Thr | Leu | Pro | Pro | Ser | Arg | Asp | Glu | Leu | Thr |
|     | 130 |     |     |     |     | 135 |     |     |     |     | 140 |     |     |     |     |
| Lys | Asn | Gln | Val | Ser | Leu | Thr | Cys | Leu | Val | Lys | Gly | Phe | Tyr | Pro | Ser |
| 145 |     |     |     |     | 150 |     |     |     |     | 155 |     |     |     |     | 160 |
| Asp | Ile | Ala | Val | Glu | Trp | Glu | Ser | Asn | Gly | Gln | Pro | Glu | Asn | Asn | Tyr |
|     |     |     |     | 165 |     |     |     |     | 170 |     |     |     |     | 175 |     |
| Lys | Thr | Thr | Pro | Pro | Val | Leu | Asp | Ser | Asp | Gly | Ser | Phe | Phe | Leu | Tyr |
|     |     |     | 180 |     |     |     |     | 185 |     |     |     |     | 190 |     |     |
| Ser | Lys | Leu | Thr | Val | Asp | Lys | Ser | Arg | Trp | Gln | Gln | Gly | Asn | Val | Phe |
|     |     | 195 |     |     |     |     | 200 |     |     |     |     | 205 |     |     |     |
| Ser | Cys | Ser | Val | Met | His | Glu | Ala | Leu | His | Asn | His | Tyr | Thr | Gln | Lys |
|     | 210 |     |     |     |     | 215 |     |     |     |     | 220 |     |     |     |     |
| Ser | Leu | Ser | Leu | Ser | Pro | Gly | Lys |     |     |     |     |     |     |     |     |
| 225 |     |     |     |     | 230 |     |     |     |     |     |     |     |     |     |     |

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FIG. 11, cont.

661 CTTCCCCCAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGT  
 -----+-----+-----+-----+-----+-----+-----+ 720  
 GAAGGGGGGTTTTGGGTTCTGTGGGAGTACTAGAGGGCCTGGGGACTCCAGTGTACGCA  
 b F P P K P K D T L M I S R T P E V T C V -  
 721 GGTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGT  
 -----+-----+-----+-----+-----+-----+-----+ 780  
 CCACCACCTGCACTCGGTGCTTCTGGGACTCCAGTTCAAGTTGACCATGCACCTGCCGCA  
 b V V D V S H E D P E V K F N W Y V D G V -  
 781 GGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGT  
 -----+-----+-----+-----+-----+-----+-----+ 840  
 CCTCCACGTATTACGGTTCTGTTTCGGCGCCCTCCTCGTCATGTTGTCGTGCATGGCACA  
 b E V H N A K T K P R E E Q Y N S T Y R V -  
 841 GGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAA  
 -----+-----+-----+-----+-----+-----+-----+ 900  
 CCAGTCGCAGGAGTGGCAGGACGTGGTCCTGACCGACTTACCGTTCCTCATGTTACGTTT  
 b V S V L T V L H Q D W L N G K E Y K C K -  
 901 GGTCTCCAACAAAGCCCTCCCAGCCCCATCGAGAAAACCATCTCCAAGCCAAAGGGCA  
 -----+-----+-----+-----+-----+-----+-----+ 960  
 CCAGAGGTTGTTTCGGGAGGGTCGGGGGTAGCTCTTTTGGTAGAGGTTTCGGTTTCCCGT  
 b V S N K A L P A P I E K T I S K A K G Q -  
 961 GCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGATGAGCTGACCAAGAACCA  
 -----+-----+-----+-----+-----+-----+-----+ 1020  
 CGGGGCTCTTGGTGTCCACATGTGGGACGGGGGTAGGGCCCTACTCGACTGGTTCTTGGT  
 b P R E P Q V Y T L P P S R D E L T K N Q -  
 1021 GGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGA  
 -----+-----+-----+-----+-----+-----+-----+ 1080  
 CCAGTCGGACTGGACGGACCAGTTTCCGAAGATAGGGTCGCTGTAGCGGCACCTCACCT  
 b V S L T C L V K G F Y P S D I A V E W E -  
 1081 GAGCAATGGGCAGCCGGAGAACAACACTACAAGACCACGCCTCCCGTGTCTGGACTCCGACGG  
 -----+-----+-----+-----+-----+-----+-----+ 1140  
 CTCGTTACCCGTCGGCCTCTTGTGTATGTTCTGGTGCAGGAGGCACGACCTGAGGCTGCC  
 b S N G Q P E N N Y K T T P P V L D S D G -  
 1141 CTCCTTCTTCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGT  
 -----+-----+-----+-----+-----+-----+-----+ 1200  
 GAGGAAGAAGGAGATGTCGTTTCGAGTGGCACCTGTTCTCGTCCACCGTCGTCCCTTGCA  
 S F F L Y S K L T V D K S R W Q Q G N V -  
 1201 CTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTC  
 -----+-----+-----+-----+-----+-----+-----+ 1260  
 GAAGAGTACGAGGCACTACGTACTCCGAGACGTGTTGGTGATGTGCGTCTTCTCGGAGAG  
 F S C S V M H E A L H N H Y T Q K S L S -  
 SalI  
 |  
 1261 CCTGTCTCCGGGTAAAtaatgtcgac 1286  
 -----+-----+-----+-----+-----+-----+  
 GGACAGAGGCCCATTtattacagctg  
 L S P G K \*

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